

10/089723

IC20 Rec'd PCT/PTO 04 APR 2002

TRANSMITTAL LETTER TO THE UNITED STATES PATENT &amp; TRADEMARK OFFICE ATTORNEY'S DOCKET NUMBER 51770

DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09673	2 October 2000	6 October 1999 24 December 1999 6 June 2000 14 June 2000 11 August 2000

TITLE OF INVENTION. MODULATORS OF CYTONKINE MEDIATED SIGNALING PATHWAY AND INTEGRIN  
 $\alpha_v\beta_3$  RECEPTOR ANTAGONISTS FOR COMBINATION THERAPY

APPLICANT(S) FOR DO/EO/US Herve GENESTE, Wilfried HORNBERGER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
  2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
  3. /X/ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
  4. /x / A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
  5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
    - a. /X/ is transmitted herewith (required only if not transmitted by the International Bureau).
    - b. / / has been transmitted by the International Bureau.
    - c. / / is not required, as the application was filed in the United States Receiving Office (RO/USO)
  6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
  7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
    - a. / / are transmitted herewith (required only if not transmitted by the International Bureau)
    - b. / / have been transmitted by the International Bureau
    - c. / / have not been made; however, the time limit for making such amendments has NOT expired.
    - d. / / have not been made and will not be made
  8. / / A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
  9. / / An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
  10. / / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
- Items 11 to 16 below concern other document(s) or information included.
11. / / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
  12. / / An assignment document for recording A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
  13. / X / A FIRST preliminary amendment  
/ / A SECOND or SUBSEQUENT preliminary amendment
  14. / / A substitute specification.
  15. / / A change of power of attorney and/or address letter.
  16. /x / Other items or information.  
International Search Report

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JC13 Rec'd PCT/PTO 04 APR 2002

U.S. Appln No (If Known) INTERNATIONAL APPLN NO  
PCT/EP00/09673

ATTORNEY'S DOCKET NO  
51770

		CALCULATIONS	PTO USE ONLY
17. /X/ The following fees are submitted			
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)).			
Search Report has been prepared by the EPO or JPO. ....	\$890.00	890.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) .....	\$710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .....	\$740.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO .....	\$1,040.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). ....	\$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT = \$		890.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than 1/20/30 months from the earliest claimed priority date (37 CFR 1.492(e)).			
Claims	Number Filed	Number Extra	Rate
Total Claims	11 -20		X\$18.
Indep. Claims	3 -3		X\$84
Multiple dependent claim(s) (if applicable)			+280
TOTAL OF ABOVE CALCULATION		=	890.
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28)			
SUBTOTAL		=	890
Processing fee of \$130. for furnishing the English translation later than 1/20/30 months from the earliest claimed priority date (37 CFR 1.492(f)) +			
TOTAL NATIONAL FEE		=	890.
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) \$40.00 per property =			
TOTAL FEES ENCLOSED		=	\$ 890.00
		Amount to be refunded \$	
		Charged \$	

a./X/ A check in the amount of \$ 890.00 to cover the above fees is enclosed

b./ I Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 11-0345. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Keil & Weinkauff  
1350 Connecticut Ave NW  
Washington, DC 20036



26474

PATENT TRADEMARK OFFICE

*Herbert B. Keil*  
SIGNATURE

Herbert B. Keil  
NAME  
Registration No. 18,967

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of )  
GENESTE et al. ) BOX PCT  
)  
International Application )  
PCT/EP 00/09673 )  
)  
Filed: October 2, 2000 )  
)

For: MODULATORS OF CYTONKINE MEDIATED SIGNALING PATHWAY AND INTEGRIN  
 $\alpha_v\beta_3$  RECEPTOR ANTAGONISTS FOR COMBINATION THERAPY

PRELIMINARY AMENDMENT

Honorable Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-identified application as follows:

IN THE CLAIMS

Kindly amend the claims as shown on the attached sheets.

R E M A R K S

The claims were amended in the preliminary examination. The claims have been amended further to eliminate multiple dependency and to place them in better form for U.S. filing. No new matter is included.

A clean copy of the claims is attached.

Favorable action is solicited.

Respectfully submitted,

KEIL & WEINKAUF



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CLEAN VERSION OF AMENDED CLAIMS - 51770

1. Use of modulators of cytokine mediated signaling pathways in combination with integrin  $\alpha_v\beta_3$  receptor antagonists for the manufacture of medicaments for the treatment or prevention of diseases.
4. Use as claimed in claim 1 wherein the modulator of cytokine mediated signalling pathways is a TNF $\alpha$  inhibitor.
11. Trade package, comprising as pharmaceutical agent a modulator of cytokine mediated signaling pathways or/and an integrin  $\alpha_v\beta_3$  receptor antagonist together with an instruction for use of this pharmaceutical agents in combination for simultaneous, separate, or temporal graduated application for the treatment or prevention of diseases.

MARKED VERSION OF AMENDED CLAIMS - 51770

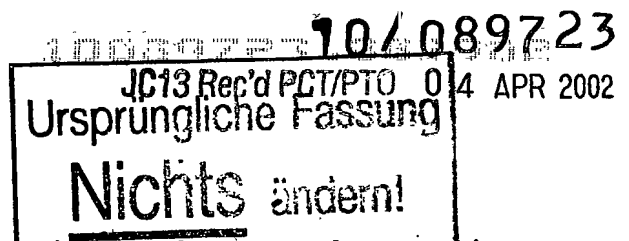
1. Use of modulators of cytokine mediated [signalling] signaling pathways in combination with integrin  $\alpha_v\beta_3$  receptor antagonists for the manufacture of medicaments for the treatment or prevention of diseases.
4. Use as claimed in claim 1 [any of claims 1 to 3] wherein the modulator of cytokine mediated signalling pathways is a TNF $\alpha$  inhibitor.
11. Trade package, comprising as pharmaceutical agent a modulator of cytokine mediated [signalling] signaling pathways or/and an integrin  $\alpha_v\beta_3$  receptor antagonist together with an instruction for use of this pharmaceutical agents in combination for simultaneous, separate, or temporal graduated application for the treatment or prevention of diseases.

CLAIMS AS FILED - OZ 51770

1. Use of modulators of cytokine mediated signaling pathways in combination with integrin  $\alpha_v\beta_3$  receptor antagonists for the manufacture of medicaments for the treatment or prevention of diseases.
2. Use as claimed in claim 1 for the treatment or prevention of inflammatory or autoimmune disorders.
3. Use as claimed in claim 2 for the treatment or prevention of rheumatoid arthritis.
4. Use as claimed in claim 1 wherein the modulator of cytokine mediated signalling pathways is a TNF $\alpha$  inhibitor.
5. Pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin  $\alpha_v\beta_3$  receptor antagonist.
6. Composition as claimed in claim 5 for use as a medicament.
7. Composition as claimed in claim 6 for curing inflammatory or autoimmune disorders.
8. Use of a composition as claimed in claim 4 for the manufacture of a medicament for the treatment or prevention of diseases.
9. Use as claimed in claim 8 for the treatment or prevention of inflammatory or autoimmune disorders.
10. Use as claimed in claim 9 for the treatment or prevention of rheumatoid arthritis.
11. Trade package, comprising as pharmaceutical agent a modulator of cytokine mediated signaling pathways or/and an integrin  $\alpha_v\beta_3$  receptor antagonist together with an instruction for use of this pharmaceutical agents in combination for simultaneous, separate, or temporal graduated application for the treatment or

CLAIMS AS FILED - OZ 51770

prevention of diseases.



Modulators of cytokine mediated signalling pathways and integrin  $\alpha_v\beta_3$  receptor antagonists for Combination Therapy

- 5 The invention relates to the use of modulators of cytokine mediated signalling pathways in combination with integrin  $\alpha_v\beta_3$  receptor antagonists for the treatment or prevention of diseases, particularly to the use of a pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an
- 10 integrin  $\alpha_v\beta_3$  receptor antagonist, for the treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheumatoid arthritis and to the pharmaceutical composition itself.

- 15 Rheumatoid arthritis (RA) is a complex chronic inflammatory disease which affects approximately 1 to 3 % of the general population. A variety of anti-inflammatory and immunosuppressive regimens have been employed to limit disease. However, significant toxicity is associated with current therapies which subdue but
- 20 ultimately fail to stop progression to erosive joint destruction.

It is known, that TNF $\alpha$ , a cytokine produced by numerous cell types, has been implicated in activating tissue inflammation and causing joint destruction in rheumatoid arthritis (see e.g.,

- 25 Moeller, A., et al. (1990) *Cytokine* 2:162-169; U.S. Patent No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B1 by Moeller, A.; WO 9729131; Tracey and Cerami, *supra*; Arend, W.P. and Dayer, J-M. (1995) *Arth. Rheum.* 38:151-160; Fava, R.A., et al. (1993) *Clin. Exp. Immunol.* 94:261-266).

30

On the other hand, it is known that cytokines, for example, IL-10 and IL-4 may have an anti-inflammatory effect. Therefore, it is believed, that compounds that suppress or inhibit proinflammatory cytokine mediated signalling pathways (anti-proinflammatory-

- 35 cytokine compounds) and compounds that stimulate anti-inflammatory cytokine mediated signalling pathways (anti-inflammatory compounds) may be useful for the treatment of RA (Bredveld, *Rheumatology* 1999, 38, 11 to 13).

- 40 Cheresch et al. describe that suppressors of angiogenesis, such as  $\alpha_v\beta_3$  antagonists, might be useful for the treatment of RA (The Journal of Clinical Investigation 1999, 103, 1, p.47 to 54; Braz. J. Med. Biol. Res. 1999, 32, p. 573 to 581).

- 45 It is an object of the present invention to provide an effective method of treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheu-



## 2

matoid arthritis, with acceptable side effects and advantageous properties.

We have found that this object is achieved by using modulators of cytokine mediated signalling pathways in combination with an integrin  $\alpha_v\beta_3$  receptor antagonist.

By combining compounds which act as modulators of cytokine mediated signalling pathways and integrin  $\alpha_v\beta_3$  receptor antagonists either in one formulation or as a kit-of-parts combination by applying both separately via the same or different routes, it is possible to achieve an inhibitory effect on inflammatory pathomechanisms causing rheumatoid arthritis significantly more pronounced than one of the two treatments alone at the given doses. The combination of modulators of cytokine mediated signalling pathways and integrin  $\alpha_v\beta_3$  receptor antagonists in doses too low to be effective alone is as least as effective as a high mono-therapy with either agent and has less potential for side-effects than one principle alone.

Therefore, the invention relates to the use of modulators of cytokine mediated signalling pathways in combination with an integrin  $\alpha_v\beta_3$  receptor antagonist for the manufacture of medicaments for the treatment or prevention of diseases, particularly of inflammatory or autoimmune disorders, particularly of rheumatoid arthritis.

Inflammatory or autoimmune disorders are, for example, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis or nephrotic syndrome.

In a preferred embodiment, the combination according to the invention can be used for the manufacture of medicaments for the treatment or prevention of rheumatoid arthritis.

Preferred modulators of cytokine mediated signalling pathways results in an anti-inflammatory effect. Therefore, according to the invention, modulators of cytokine mediated signalling pathways preferred are compounds that suppress or inhibit proinflammatory cytokine mediated signalling pathways (anti-proinflammatory-cytokine compounds),

such as, for example,  $\text{TNF}\alpha$ -inhibitors, particularly  $\text{TNF}\alpha$ -antibodies, inhibitors of interleukin- $1\beta$  converting enzyme (ICE inhibitors), inhibitors of Interleukin 1 (IL-1 inhibitors) such as IL-1RA (IL-1 receptor antagonist, Synergen/Amgen), inhibitors of

- Interleukin 2 (IL-2 inhibitors) such as anti-IL2R antibodies, DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins, Seragen, see e.g., *Arthritis & Rheumatism* (1993) Vol. 36, 1223) or Anti-Tac (humanized anti-IL-2Ra, Protein Design Labs/Roche), inhibitors of
- 5 Interleukin 6 (IL-6 inhibitors), inhibitors of Interleukin 12 (IL-12 inhibitors), inhibitors of Interleukin 17 (IL-17 inhibitors, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S120), inhibitors of Interleukin 18 (IL-18 inhibitors) or antiinflammatory or antiautoimmune drugs such as R973401
- 10 (phosphodiesterase Type IV inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282), MK-966 (COX-2 Inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S81), Iloprost (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S82), methotrexate, thalido-
- 15 mide (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282) and thalidomide-related drugs (e.g., Celgen), leflunomide (anti-inflammatory and cytokine inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S131, *Inflammation Research* (1996) Vol. 45, pp. 103-107), tranexamic
- 20 acid (inhibitor of plasminogen activation, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S284), T-614 (cytokine inhibitor, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282), prostaglandin E1 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282),
- 25 Tenidap (non-steroidal anti-inflammatory drug, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S280), Naproxen (non-steroidal anti-inflammatory drug, see e.g., *Neuro Report* (1996) Vol. 7, pp. 1209-1213), Meloxicam (non-steroidal anti-inflammatory drug), Ibuprofen (non-steroidal anti-inflammatory
- 30 drug), Piroxicam (non-steroidal anti-inflammatory drug), Diclofenac (non-steroidal anti-inflammatory drug), Indomethacin (non-steroidal anti-inflammatory drug), Sulfasalazine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S281), Azathioprine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39,
- 35 No. 9 (supplement), S281), zap-70 and/or lck inhibitor (inhibitor of the tyrosine kinase zap-70 or lck), VEGF inhibitor and/or VEGF-R inhibitor (inhibitors of vascular endothelial cell growth factor or vascular endothelial cell growth factor receptor, inhibitors of angiogenesis), corticosteroid anti-inflammatory drugs
- 40 (e.g., SB203580), gold, penicillamine, chloroquine, hydroxychloroquine, chlorambucil, cyclophosphamide, cyclosporine, total lymphoid irradiation, anti-thymocyte globulin, anti-CD4 antibodies, CD5-toxins, collagen, lobenzarit disodium, Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.),
- 45 ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302, Isis Pharmaceuticals, Inc.), soluble complement receptor 1 (TP10, T Cell Sciences, Inc.), prednisone, orgotein, glycosamino-

5 globulin, zileuton, mycophenolic acid (RS-61443), tacrolimus (FK-506), sirolimus (rapamycin), amiprilose (therafectin), cladribine (2-chlorodeoxyadenosine) or azaribine

## 10 signalling pathways (anti-inflammatory compounds)

15 e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S296), interleukin-13 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S308) or IL-4-, IL-10-, IL-11 or IL-13 agonists (e.g., agonist antibodies).

20 Inhibitors are preferred low molecular molecules, antisense molecules or mono or polyclonal antibodies.

25 enzyme (ICE inhibitors) or inhibitors of IL-12 or IL-18, most preferred modulators of cytokine mediated signalling pathways are TNF $\alpha$  inhibitors, particularly TNF $\alpha$  antibodies.

Preferred ICE Inhibitors within the scope of the invention are  
30 compounds which have a  $K_i$  value of  $1\mu\text{M}$  or less. Most preferred are  
those ICE Inhibitors which have a  $K_i$  value of  $100\text{nM}$  or less and  
mostly preferred are those ICE Inhibitors which have a  $K_i$  value of  
 $10\text{nM}$  or less.

35 Suitable for the combination therapy of the invention are in principle all ICE inhibitors, for example such as L-Alaninamide (N-((phenylmethoxy)carbonyl)-L-valyl-N-((1S)-3-((2,6-dichlorobenzoyl)oxy)-1-(2-ethoxy-2-oxoethyl)-2-oxopropyl), SDZ-224-015, VE-13045.

40 Novartis); 6a,12a-epoxy-1,2,3,4,6a,7,12,12a-octahydro-3,7-dihydroxy-8-methoxy-3-methyl-benz(a)anthracen-1,12-dione (El-1507-1, El-1507-2, Kyowa Hakko), VX-740, HMR-3480 (Aventis, Pharmaprojects databases), N-(N-((2S,3S)-3-trans-carboxyoxirane-2-carbonyl)-L-phenylalanyl)-1,4-diaminobutane (TAN-1756A, TAN-1756B, Ta-  
45 keda), (2S-cis)-5-(Benzyloxycarbonylamino-1,2,4,5,6,7-hexahy-

dro-4-(oxoazepino(3,2,1-hi)indole-2-carbonyl)-amino)-4-oxobutanoic acid, Idun (US).

Suitable for the combination therapy of the invention are in principle all TNF $\alpha$  inhibitors, such as TNF $\alpha$  antibodies, TNF $\alpha$ -convertase inhibitors or the compounds SR-31747 (Cyclohexanamine, N-(3-(3-chloro-4-cyclohexylphenyl)-2-propenyl)-N-ethyl-, hydrochloride, (Z)-(CAS), Sanofi-Synthelabo, Pharmaprojects databank), 75 kD TNFR-IgG (75 kD TNF receptor-IgG fusion protein, Immunex; see e.g., *Arthritis & Rheumatism* (1994) Vol. 37, S295; *J. Invest. Med.* (1996) Vol. 44, 235A), 55 kD TNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche), TNF-bp/s-TNFR (soluble TNF binding protein; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement)).

More preferred TNF $\alpha$  inhibitors are TNF $\alpha$  antibodies, for example as described in EP 186833 B1, EP 614984, EP 516785, EP 626389, EP 492488, EP 351789, EP 659766, WO 9429347, EP 701571, EP 486526, WO 9216553, EP 610201, EP 366043, US 5672347, US 5795967, US 5807715, EP 260610 B1 or WO 9729131.

Most preferred TNF $\alpha$  antibodies are poly- or monoclonal, human, humanized, murine or chimeric TNF $\alpha$  antibodies such as CDP-571/Bay-10-3356 (humanized TNF $\alpha$  antibody, Celltech/Bayer), cA2 (chimeric TNF $\alpha$  antibody, Centocor), S284; *Amer. J. Physiol. - Heart and Circulatory Physiology* (1995) Vol. 268, pp. 37-42), D2E7 (WO 9729131, Knoll AG), MAK 195 (EP 260610, BASF Aktiengesellschaft), Synergen (AmgenWorld, Scrip 1997, 2216, 26), Yeda (Ares-Serono, Scrip 1992, 1687, 24), BB-2983 (Glaxo Wellcome, Pharmaprojects database), AGT1 (Advanced Biotherapy Concepts), STNF-R1 (Amgen, Scrip Daily Online, 22 Nov. 1999) or TNF-484 (Novartis, Pharmaprojects database), particularly D2E7.

Further preferred TNF $\alpha$  antibodies are antibodies, or an antigen-binding portion thereof, that dissociates from human TNF $\alpha$  with a  $K_d$  of  $1 \times 10^{-8}$  M or less and a  $K_{off}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human TNF $\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less. More preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNF $\alpha$  with a  $K_{off}$  of  $5 \times 10^{-4} \text{ s}^{-1}$  or less, or even more preferably, with a  $K_{off}$  of  $1 \times 10^{-4} \text{ s}^{-1}$  or less. More preferably, the antibodies, or antigen-binding portion thereof, neutralizes human TNF $\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an  $IC_{50}$  of  $1 \times 10^{-8}$  M or less, even more preferably with an  $IC_{50}$  of  $1 \times 10^{-9}$  M or

less and still more preferably with an  $IC_{50}$  of  $5 \times 10^{-10}$  M or less.

A "neutralizing antibody", as used herein (or an "antibody that  
5 neutralized hTNF $\alpha$  activity"), is intended to refer to an antibody whose binding to hTNF $\alpha$  results in inhibition of the biological activity of hTNF $\alpha$ . This inhibition of the biological activity of hTNF $\alpha$  can be assessed by measuring one or more indicators of hTNF $\alpha$  biological activity, such as hTNF $\alpha$ -induced cytotoxicity  
10 (either *in vitro* or *in vivo*), hTNF $\alpha$ -induced cellular activation and hTNF $\alpha$  binding to hTNF $\alpha$  receptors. These indicators of hTNF $\alpha$  biological activity can be assessed by one or more of several standard *in vitro* or *in vivo* assays known in the art. Preferably, the ability of an antibody to neutralize hTNF $\alpha$  activity is assessed  
15 by inhibition of hTNF $\alpha$ -induced cytotoxicity of L929 cells. As an additional or alternative parameter of hTNF $\alpha$  activity, the ability of an antibody to inhibit hTNF $\alpha$ -induced expression of ELAM-1 on HUVEC, as a measure of hTNF $\alpha$ -induced cellular activation, can be assessed.

20 The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the  
25 BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ). For further descriptions, see Example 1 and Jönsson, U., et al. (1993) *Ann. Biol. Clin.* 51:19-26; Jönsson, U., et al. (1991) *Biotechniques* 11:620-627; Johnsson, B., et al. (1995) *J. Mol. Recognit.* 8:125-131; and Johnsson, B., et al. (1991)  
30 *Anal. Biochem.* 198:268-277.

The term " $K_{off}$ ", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

35

The term " $K_d$ ", as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction.

40 Preferred integrin  $\alpha_v\beta_3$  receptor antagonists within the scope of the invention are substances which show an  $IC_{50}$  value of 100nM or less for the inhibition of vitronectin binding to integrin  $\alpha_v\beta_3$  in an ELISA assay, which is, described for example in DE 19919218.9 (German application number).

45

Suitable integrin  $\alpha_v\beta_3$  receptor antagonists for the combination therapy of the invention are, in principle, all integrin  $\alpha_v\beta_3$  receptor antagonists, for example as described in Pitts et al.; J. Med. Chem. 2000, 43, 27-40; Batt et al., J. Med. Chem. 2000, 43, 41-51; Miller et al., Bioorg. Med. Chem. Lett. 9, 1999, 1807-1812; Keenan et al., Bioorg. Med. Chem. Lett. 9, 1999, 1801-1806; Rockwell et al., Bioorg. Med. Chem. Lett. 9, 1999, 937-942; Samanen et al., Current Pharm. Design 1997, 3, 545-584; Miller et al., J. Med. Chem. 2000, 43, 22-26; Hartmann and Dugan, Exp. Opin. Invest. Drugs 2000, 9 (6), 1281-1291; Miller et al., Drug Discovery Today 2000, 5 (9), 397-408; DE 19919218.9 (German application number), DE 19948269.1 (German application number), DE 19962998.6 (German application number), DE 10027514.1 (German application number), DE 10028575.9 (German application number), DE 10039998.3 (German application number), WO 9952879, WO 9835917, WO 0000486, WO 0017197, WO 0031067, WO 9843962, WO 9926945, WO 9950249, WO 9958162, WO 0000481, US 6056958, WO 43787, WO 9637492, WO 9723480, WO 9733887, WO 9748395, WO 9748444, WO 9823608, US 5,849,736, DE 19626701, EP 0796855A1, DE 19653645, DE 19653646, DE 19653647, EP 796855, EP 820988, EP 820991, EP 853084, EP 854145, US 5990145, WO 9915506, WO 9915507, WO9932457, WO 9937621, WO 9959992, EP 928790, EP 928793, US 6001855, WO 00024724, WO 9825892, WO 9965944, WO 0048603, WO 9938849, WO 9952872, DE 19534016, DE 19548709, DE 19653036, DE 19654483, DE 19705450, DE 1971300, DE 19725368, DE 19842415, DE 19850131, EP 683173, EP 710657, EP 741133, EP 771 818, WO 9714716, WO 9723451, WO 9738009, WO 9744333, WO 9800395, WO 9818764, WO 9827112, WO 9835949, WO 9901472, WO 9910371, WO 9931126, WO 0003973, WO 0026212, WO 9532710, WO 9726250, WO 9737655, WO 9808518, WO 9808840, WO 9818460, WO 9818461, WO 9831359, WO 9844797, WO 9846220, WO 9901472, WO 9930709, WO 9930713, WO 9931061, WO 9931099, WO 0006169, WO 0009503, US 5981546, US 6017925, US 6017926, WO 9967230, WO 9734865, FR 2768734-A1, FR 2768736-A1, WO 0032578, US 5639765, US 5681820, US 5852210, US 5972986, US 6013651, WO 9708145, WO 9736858, WO 9736859, WO 9736860, WO 9736861, WO 9736862, WO 9944985, WO 9944994, WO 9951638, WO 9952896, WO 0009143, WO 0038665, WO 0038715, WO 0038719, WO 0038786, WO 9600574, WO 9600730, WO 9606087, WO 9626190, WO 9701540, WO 9724119, WO 9724122, WO 9724124, WO 9724336, WO 9814192, WO 9815278, WO 9829561, WO 9830542, WO 9840488, WO 9905107, WO 9906049, WO 9911626, WO 9915170, WO 9915178, WO 9915508, WO 9945927, WO 0007544, WO 0033838 or WO 9933798, particularly, the following proteins, peptidic and nonpeptidic compounds.

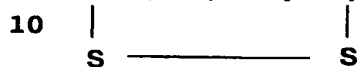
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Proteins and peptidic integrin  $\alpha_v\beta_3$  receptor antagonists:

LM 609 (vitaxin, Pharmaprojects),  
 abciximab (c7E3 Fab, Reopro®, Pharmaprojects),  
 Peptides and peptidomimetics of Arg-Gly-Asp and derivatives thereof like:

- 5 cyclo(RGDfV), As-Pen-RGDC-OH, cyclo[RGD-Mamb-P], XJ 735  
 (cyclo[R-G-D-Mamb-A]), XK 002 (cyclo[(NMe)R-G-D-(2-amino-1,3-thiazol-4-yl-acetic acid)-V]), DMP 728  
 (cyclo[[(NMe)R-G-D-Mamb-DAbu]), SK+F 107260

Mba-(NMe)R-Gly-Asp-Man



EMD 121974 (cyclo[R-G-D-f-(NMe)V]) and any other RGD containing peptides.

- 15 Non-peptidic integrin  $\alpha_v\beta_3$  receptor antagonists:  
 (2R)-2-[(2R)-2-{3-[(3-{[amino(imino)methyl]amino}propanoyl)amino]phenyl}-3-carboxy propanoyl)amino]-3-methylbutanoic acid, 3-[8-(2-{[amino(imino)methyl]amino}ethyl)-1-benzyl-2-oxo-1,2,3,5-tetrahydro-4H-1,4-benzodiazepin-4-yl]propanoic acid, 2,3-dihydroxypropyl 2-[(benzyloxy)carbo-  
 20 nyl]amino}-4-({9,10-dimethoxy-4-[(E)-2-(1,4,5,6-tetrahydropyrimidin-2-yl)hydrazono]-1,2,3,3a,4,5,6,10b-octahydrobenzo[e]azulen-8-yl}oxy)butanoate, (2S)-2-[(benzyloxy)carbo-  
 25 nyl]amino}-3-[(4S)-4-[3-(4,5-dihydro-1H-imidazol-2-ylamino)propyl]-2,5-dioxoimidazolidin-1-yl]acetyl)amino]propanoic acid, L-7418415 ((2S)-2-[(phenylsulfonyl)amino]-3-({4-[2-(1,4,5,6-tetrahydropyrimidin-2-ylamino)ethoxy]benzoyl}amino)propanoic acid), (2S)-2-[(4-isobutylphenyl)sulfonyl]amino}-3-[(5-[3-(pyridin-2-ylamino)propyl]-4,5-dihydroisoxazol-3-yl}carbo-  
 30 nyl)amino]propanoic acid, (2S)-2-[(benzyloxy)carbo-  
 nyl]amino}-3-[(4-[4-(4,5-dihydro-1H-imidazol-2-ylamino)butanoyl]piperazin-1-yl}carbonyl)amino]propanoic acid, (2S)-2-[(benzyloxy)carbonyl]amino}-3-[(4-[4-(4,5-dihydro-1H-imidazol-2-ylamino)propanoyl]piperazin-1-yl}carbonyl)amino]propanoic acid, SD-186 ((2S)-2-[(phenylsulfonyl)amino]-3-[(8-(pyridin-2-ylamino)methyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-3-yl]carbo-  
 35 nyl)amino]propionic acid), SD-183 ((2S)-2-[(phenylsulfonyl)amino]-3-[(8-(pyridin-2-ylamino)methyl)-1-oxa-2-azaspiro[4.5]dec-2-en-3-yl]carbonyl)-amino]propanoic acid, SD-983 ((2S)-2-[(benzyloxy)carbonyl]amino}-3-[(3-[3-(4,5-dihydro-1H-imidazol-2-ylamino)propoxy]isoxazol-5-yl}carbonyl)amino]propanoic acid), XT-199 ((2S)-3-[(3-[3-(4,5-dihydro-1H-imidazol-2-ylamino)propoxy]isoxazol-5-yl}carbonyl)amino]-2-[(phenylsulfo-  
 40 nyl)amino]propanoic acid), SG-545 (Methyl (2S)-2-[(benzyloxy)carbonyl]amino}-3-[(3-[3-(4,5-dihydro-1H-imidazol-2-ylamino)propoxy]isoxazol-5-yl}carbonyl)amino]propanoic acid), SM 256

- 40

LM 609 (vitaxin), EMD 121974 (cyclo[R-G-D-f-(NMe)V]),

SB 265123 ([ (10S)-3-[3-(pyridin-2yl-amino)propoxy]-10,11-dihy-

45 dro-5H-dibenzo[a,d]-cyclohepten-10yl]acetic acid), SB 267268



## 10

- (((4S)-3-oxo-8-[3-(pyridin-2-ylamino)propoxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-4-yl]acetic acid), SB 273005 (Lark et al.; 21<sup>st</sup> Ann. Meet. Amer. Soc. Bone Mineral Res., 30.9.-4.10.1999; SU201), SC 68448 (N-[[3-{{amino(imino)methyl}amino}benzoyl]amino]acetyl}-3-(3,5-dichlorophenyl)- $\beta$ -alanine), SC 69000 (4-[(3-{{amino(imino)methyl}amino}benzoyl]amino]-N-(isobutoxycarbonyl)phenylalanine and SC-65811 (N-[[3-{{(benzylamino)carbonyl}amino}benzoyl]amino]acetyl}-3-pyridin-3-yl-L-alanine).
- 10 All mentioned compounds can also be applied as prodrugs. Prodrugs are substances which metabolise in vivo to the active compound. Examples for such metabolism are first pass metabolisms (e.g. esters to free acids or carboxylates).

- 15 "Orally available" means at least 10%, preferred 30% and more preferred 50% for integrin  $\alpha_v\beta_3$  receptor antagonist.

All mentioned compounds may be administered as such or in the form of their salts with physiologically tolerated acids or bases. Antibodies may also be used as antibody-fragments.

- Preferred combinations of modulators of cytokine mediated signalling pathways with integrin  $\alpha_v\beta_3$  receptor antagonists are selected from the preferred modulators of cytokine mediated signalling pathways and the preferred integrin  $\alpha_v\beta_3$  receptor antagonists.

- The modulators of cytokine mediated signalling pathways in combination with the integrin  $\alpha_v\beta_3$  receptor antagonist may be administered together in a pharmaceutical composition or simultaneously via separate ways or separate or temporal graduated.

Therefore, the invention further relates to a pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin  $\alpha_v\beta_3$  receptor antagonist.

- 35 This composition can be used as a medicament, particularly for curing or preventing inflammatory or autoimmune disorders, such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoimmune uveitis or nephrotic syndrome.

In a preferred embodiment, the composition is used for the treatment or prevention of rheumatoid arthritis.

- 45 The compounds of the invention can be administered orally or parenterally in a conventionally way (subcutaneously, intravenously, intramuscularly, intraperitoneally, rectally). Administration

tion can also take place with vapours or sprays through the nasopharyngeal space. Oral administration is preferred.

The dosage depends on age, condition and weight of the patient  
5 and on the mode of administration. The two compounds can be formulated in a single pharmaceutical form or in separate pharmaceutical forms. Administration can be given in several single doses (e.g. 2 to 4) or once or twice a day as depot form.

- 10 The weight ratio of integrin  $\alpha_v\beta_3$  receptor antagonist to modulators of cytokine mediated signalling pathways conveniently is in the range of 1:100 to 100:1 preferably 1:10 to 10:1. Advantageously, the dosage to be administered by means of a combination per day and kg amounts to 0,05 to 20 mg of an integrin  
15  $\alpha_v\beta_3$  receptor antagonist and 0,1 to 20 mg, preferably 1 to 10 mg of an modulator of cytokine mediated signalling pathways. In general, the total amount of an integrin  $\alpha_v\beta_3$  receptor antagonist and an modulators of cytokine mediated signalling pathways to be administered daily amounts per kg to a maximum of 50 mg. When a  
20 hydrate or a pharmaceutically usable salt is used, then the above values are to be appropriately adjusted.

- The compounds can be used individually or together in conventional solid or liquid pharmaceutical forms, e.g. as uncoated or  
25 (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. In these, the active substances can be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators,  
30 plasticizers, wetting agents, dispersants, emulsifiers, solvents, release slowing agents, antioxidants and/ or propellant gases (cf. H. Sucker et al. Pharmaceutische Technologie, Thieme Verlag, Stuttgart, 1978). The administration form obtained in this way normally comprises the active substance  
35 in an amount of from 0.1% to 99% by weight.

- Treatment of a patient with an inflammatory or autoimmune disease by a combination, composition and method according to the present invention may include concomitant use of further adjunctive  
40 agents, such as antiinflammatory drugs as described above.

- Subject of the present invention are also pharmaceutical compositions, comprising an integrin  $\alpha_v\beta_3$  receptor antagonist in an appropriate container and an modulator of cytokine mediated signalling pathways in a separate container to be used according to the  
45 above-mentioned administration regiments.

Pharmaceutical packaging units prepared in accordance with the present invention may consist of an appropriate administration form comprising the integrin  $\alpha_v\beta_3$  receptor antagonist, and an appropriate packaging unit comprising the modulator of cytokine mediated signalling pathways. The two active compounds are preferably present in the packaging unit in two different containers, e.g. tablets. However, depending on the type of active compound, it may also be possible to provide both compounds in a single dosage form. Further, the pharmaceutical packaging units comprise instructions, for example in the form of a package leaflet prescribed for medicaments from which it follows that the administration of a therapeutically active amount of the integrin  $\alpha_v\beta_3$  receptor antagonist advantageously takes place in combination with administration of an modulators of cytokine mediated signalling pathways.

If applied separately, the administration of the modulators of cytokine mediated signalling pathways takes places before, simultaneously or after the administration of the integrin  $\alpha_v\beta_3$  receptor antagonist.

Information regarding the manner of use can either be given in the information leaflet or as a packing overprint on the medical preparation which can be bought together with medicinal preparations which comprise integrin  $\alpha_v\beta_3$  receptor antagonists. On the one hand, pharmaceutical packaging units comprising only appropriate administration forms of the integrin  $\alpha_v\beta_3$  receptor antagonists can comprise such information e.g. in the form of package leaflets, wherein the combined administration together with modulators of cytokine mediated signalling pathways according to the present invention is mentioned. On the other hand, pharmaceutical packaging units comprising only modulators of cytokine mediated signalling pathways can comprise such information wherein the combined administration together with integrin  $\alpha_v\beta_3$  receptor antagonists and the use according to the present invention is mentioned. A third alternative would be to provide pharmaceutical packaging units comprising an integrin  $\alpha_v\beta_3$  receptor antagonist, modulators of cytokine mediated signalling pathways and an appropriate information about the combined use of both, e.g. the usual package leaflet.

Therefore, the invention further relates to a pharmaceutical trade package, comprising as pharmaceutical agent an modulator of cytokine mediated signalling pathways or/and an integrin  $\alpha_v\beta_3$  receptor antagonist together with an instruction for use of this pharmaceutical agents in combination for simultaneous, separate,

or temporal graduated application for the treatment or prevention of diseases.

Appropriate directions of use of the above-mentioned pharmaceutical agents are essential for commercialization of such pharmaceutical packages, comprising either the integrin  $\alpha_v\beta_3$  receptor antagonist, the modulator of cytokine mediated signalling pathways or a combination thereof.

Commercialization of appropriate pharmaceuticals by pharmaceutical companies is only possible when prior approval of such pharmaceutical agents and the respective administration regimens is achieved by the respective national Health Authorities, such as the FDA in the US or the CPMP Authority in Europe.

This includes but is not limited to performing clinical trials according to well-established procedures under the supervision of said pharmaceutical company which later on intends to commercialize such pharmaceutical agents. This also includes filing of appropriate documentation about the results of such clinical trials with the respective Health Authority in order to get marketing approval. The approval is in many cases restricted to certain administration protocols or regimens which have to be included in printed form in the accompanying information leaflet prescribed for medicaments.

#### Examples

##### Example 1

Polyarthrititis model in Tg197 transgenic mice

Transgenic mice (Tg197), which have been shown to express human wild type TNF $\alpha$  (modified in the 3' region beyond coding sequences) develop chronic polyarthrititis with 100 % incidence at 4 - 7 weeks of age (See WO 9729131, Example DIII).

Transgenic mice are first identified by PCR at 3 days of age and then are verified by slot blot hybridization analysis at 15 days of age. From the first week of age, litters of transgenic mice are divided into groups of 8 animals each. Before the first weekly injection, average body weight are determined by weighing, all animals in each group and calculating the average body weight. The date and weights of all animals in each group are recorded once a week in the log book.

Each group receive one i.p. injection of a TNF $\alpha$  inhibitor, for example a TNF $\alpha$  antibody, for example D2E7 (see WO 9729131) (dose range 0.1 - 10  $\mu$ g/g) or per week

or vehicle.

- 15 A litter with non transgenic mice is also included in the study  
to serve as a control (Group 7 - nontransgenic; no treatment)

phology are recorded weekly for each animal. Arthritic scores

- 20 were recorded as follows; 0 = No arthritis, (normal appearance and flexion); + = mild arthritis joint distortion); ++ = moderate arthritis (swelling, joint deformation) and +++ = heavy arthritis (ankylosis detected on flexion and severely impaired movement).

- 25 Sera are collected from 4 out of 8 mice per group by orbital sinus bleeding at 5 weeks of age. At completion of the study all animals are sacrificed and sera are collected by cardiac puncture and stored at -70 °C.

- 30 Treatment is continued for 8 weeks. At 9 weeks of age, all mice are sacrificed and ankle joints are collected in formalin. Ankle joint sections were then stained with haematoxylin/eosin and histopathology scores are evaluated microscopically in a series of sections. Histopathological scoring based on haematoxylin/eosin staining of joint sections is based as follows; 0 = No detectable disease; 1 proliferation of the synovial membrane; 2 = heavy synovial thickening, 3 = cartilage destruction and bone erosion.

Levels of integrin  $\alpha V\beta 3$  antagonists are determined by HPLC. Le-

- 40 vels of TNF $\alpha$  inhibitor, for example a TNF $\alpha$  antibody, for example D2E7 are determined by EIA according to the validated PK assay (MPF/EB 9644) with one modification. Biotinylated MAK195F is used instead of biotinylated D2E7 in order to eliminate the interference from murine anti-human antibodies. Levels of murine anti
- 45 human antibodies (MAHA) are determined in a direct ELISA. Microtiter plates were coated with 10  $\mu$ g/ml of LU 200134 overnight at 4  $^{\circ}$ C, and blocked with 3 % teleostean gelatin (Sigma, Cat # G7765)

for 2 hours at 25 °C. Diluted serum samples or a standard mouse anti-human antibody (Sigma, Cat # M-9035 ) are added to the plates and incubated overnight at 4 °C. Biotinylated D2E7 at 5 nM is added and incubated for 2 hours at 4 °C. Plates are washed 5 times with PBS between each step. Avidin coupled alkaline phosphatase (Boehringer Mannheim) are added at 115000 dilution and incubated for 1 hour at 4 °C. Bound avidin-alkaline phosphatase is measured with an enzyme amplification kit (TMB, Pierce, Cat # 1854050) according to manufacturer's instructions. ODs are recorded at 490 nm, and the levels of MAHA are assigned from the standard curve.

ED<sub>50</sub> calculations: For each week, means and standard errors of arthritic scores are plotted as a function of dose. ED<sub>50</sub> values are calculated with a non-linear four parameter curve fitting. Histo-  
25 pathological scores determined after the mice have been sacrificed at week 9 are also plotted as a function of dose and ED<sub>50</sub> value is derived similarly.

The use of the combination of a modulator of cytokine mediated signalling pathways and an integrin  $\alpha_v\beta_3$  receptor antagonists achieves an inhibitory effect on inflammatory pathomechanisms causing rheumatoid arthritis significantly more pronounced than one of the two treatments alone at the given doses. The combination of a modulator of cytokine mediated signalling pathways and an integrin  $\alpha_v\beta_3$  receptor antagonists in doses too low to be effective alone is effective as a high mono-therapy with either agent and has less potential for side-effects than one principle alone.

## Claims

1. Use of modulators of cytokine mediated signalling pathways  
5 in combination with integrin  $\alpha_v\beta_3$  receptor antagonists for the manufacture of medicaments for the treatment or prevention of diseases.
2. Use as claimed in claim 1 for the treatment or prevention of  
10 inflammatory or autoimmune disorders.
3. Use as claimed in claim 2 for the treatment or prevention of rheumatoid arthritis.
- 15 4. Use as claimed in any of claims 1 to 3 wherein the modulator of cytokine mediated signalling pathways is a TNF $\alpha$  inhibitor.
5. Pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin  $\alpha_v\beta_3$  receptor antagonist.  
20
6. Composition as claimed in claim 5 for use as a medicament.
7. Composition as claimed in claim 6 for curing inflammatory or  
25 autoimmune disorders.
8. Use of a composition as claimed in claim 4 for the manufacture of a medicament for the treatment or prevention of diseases.  
30
9. Use as claimed in claim 8 for the treatment or prevention of inflammatory or autoimmune disorders.
10. Use as claimed in claim 9 for the treatment or prevention of  
35 rheumatoid arthritis.
11. Trade package, comprising as pharmaceutical agent a modulator of cytokine mediated signalling pathways or/and an integrin  $\alpha_v\beta_3$  receptor antagonist together with an instruction for use  
40 of this pharmaceutical agents in combination for simultaneous, separate, or temporal graduated application for the treatment or prevention of diseases.

Modulators of cytokine mediated signalling pathways and Integrin  $\alpha_v\beta_3$  receptor antagonists for Combination Therapy

5 Abstract

The invention relates to the use of modulators of cytokine mediated signalling pathways in combination with integrin  $\alpha_v\beta_3$  receptor antagonists for the treatment or prevention of diseases, particularly to the use of a pharmaceutical composition, comprising a modulator of cytokine mediated signalling pathways and an integrin  $\alpha_v\beta_3$  receptor antagonist, for the treatment or prevention of inflammatory or autoimmune disorders, particularly for the treatment or prevention of rheumatoid arthritis and to the pharmaceutical composition itself.

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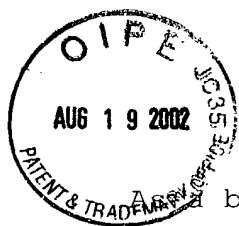
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## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

## MODULATORS OF CYTONKINE MEDIATED SIGNALING PATHWAY AND INTEGRIN $\alpha_v\beta_3$ RECEPTOR ANTAGONISTS FOR COMBINATION THERAPY

the specification of which:

[ ] is attached hereto.

[x] was filed on \_\_\_\_\_ as 10/089,723

[x] was filed as PCT/EP00/09673 on October 2, 2000

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

[ ] In compliance with this duty, attached is an information disclosure statement.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
			Yes	No
<u>199 48 269.1</u>	<u>Germany</u>	<u>10/6/99</u>	[X ]	[ ]
Number	Country	Date Filed		
<u>199 62 998.6</u>	<u>Germany</u>	<u>12/24/99</u>	[X ]	[ ]
Number	Country	Date Filed		
<u>100 27 514.1</u>	<u>Germany</u>	<u>6/6/00</u>	[X ]	[ ]
Number	Country	Date Filed		
<u>100 28 575.9</u>	<u>Germany</u>	<u>6/14/00</u>	[X ]	[ ]
Number	Country	Date Filed		



[ ]

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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2-00

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Full name of second inventor



Inventor's signature

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